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Gender and Time to Arrival among Ischemic Stroke Patients in the Greater Cincinnati/Northern Kentucky Stroke Study

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Abstract

Background—Some studies of stroke patients report longer pre-hospital delays in women, but others conflict; studies vary in their inclusion of factors including age and stroke severity. We aimed to investigate the relationship between gender and time to emergency department (ED) arrival and the influence of age and stroke severity on this relationship.

Methods—Ischemic stroke patients ≥ 20 years old who presented to 15 hospitals within a 5-county region of Greater Cincinnati/Northern Kentucky during 2010 were included. Time from

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CONFLICTS OF INTEREST/DISCLOSURES

Dawn Kleindorfer is a consultant for Genentech.

Dr. Felipe De Los Rios La Rosa is a member of Boehringer Ingelheim speaker's bureau.

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Dr. Matthew Flaherty is on the speaker's bureau for CSL Behring and Janssen. He is the principal investigator of a phase II NINDS funded treatment trial of intracerebral hemorrhage, study drug supplied by Novo Nordisk, and receives research support from a Bristol-Myers Squibb/Pfizer Medical Educational Grant.

symptom onset to ED arrival and covariates were abstracted by study nurses and reviewed by study physicians. Data were analyzed using logistic regression with time to arrival dichotomized at ≤ 3 hours, in the overall sample and then stratified by NIHSS and age.

Results—1991 strokes (55% women) were included. Time to arrival was slightly longer in women (geometric mean 337 minutes [95%CI 307–369] vs. 297 [95%CI 268–329], p =0.05), and 24% of women vs. 27% of men arrived within 3 hours (p=0.15). After adjusting for age, race, NIHSS, living situation, and other covariates, gender was not associated with delayed time to arrival (OR=1.00, 95%CI 0.78–1.28). This did not change across age or NIHSS categories.

Conclusions—After adjusting for factors including age, NIHSS, and living alone, women and men with ischemic stroke had similar times to arrival. Arrival time is not likely a major contributor to differences in outcome between men and women.

Keywords

gender; stroke; ischemic; acute stroke; delay

INTRODUCTION

Some studies of acute ischemic stroke (AIS) patients report longer times from symptom onset to emergency department (ED) arrival for women,[1–5] but other studies report no significant difference in time to ED arrival between women and men.[6–11] The relationship between gender and time to ED arrival in AIS is important to clarify given worse short- and long-term outcomes in women and was highlighted as an issue in the recently published stroke prevention guidelines for women by Bushnell et al.[6,12–14] In addition, in some study populations, women are less likely than men to receive standard-of-care therapies for acute ischemic stroke, and delayed time to arrival is the most common reason for exclusion from acute time-sensitive therapies in both genders.[1,5,7,15]

In previous studies investigating time to arrival by gender, factors that differ by gender and may affect time to ED arrival (e.g. presenting symptoms, stroke severity, and living arrangement) are not consistently included as potential confounders. Patient age is commonly included as a confounding variable in studies that investigate time to ED arrival among AIS patients, but National Institute of Health Stroke Scale (NIHSS) score is often omitted, and living situation is rarely included.[2,3,5,9] In addition, not all studies of factors leading to delayed ED arrivals in stroke patients have used the same criteria with regard to their inclusion or exclusion of patients with unknown times of symptom onset.[4,8,9,11] Overall, previously published data on gender and time to ED arrival have not systematically evaluated the effects of age and stroke severity on the relationship of gender and time to arrival.

Objectives

The primary objective of our study was to investigate and further clarify the relationship between gender and time to ED arrival, with a focus on the influence of age and stroke severity on this relationship. The secondary objectives of our study were: 1) to evaluate additional predictors of delayed ED arrival including presenting symptoms and living

situation; and 2) to evaluate whether known predictors of delayed ED arrival vary by stroke severity and age.

METHODS

AIS patients at least 20 years of age who were residents of a 5-county region of Greater Cincinnati/Northern Kentucky and who presented to one of the 15 area hospital EDs during 2010 were included in the study. Diagnoses of stroke were obtained through retrospective review of patients' data. Following screening for strokes using discharge ICD-9 codes, all cases of stroke were verified by study physicians using chart abstraction forms, images, and reports. More detailed methodology regarding the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) has been published previously.[16] The Institutional Review Board for each participating hospital approved the study.

Data Collection

Time of symptom onset and time of ED arrival, as well as data on all covariates, were abstracted by research nurses and reviewed by study physicians. If the exact time of symptom onset was unknown, the last seen normal time was used to calculate time from symptom onset to ED arrival. If both time of onset and time last seen normal were unknown, the time to arrival was considered greater than 3 hours.

Covariates included in the analysis were age, initial National Institute of Health Stroke Score determined retrospectively (rNIHSS),[17] Black race, insurance status, marital status, living situation, EMS use (yes/no), presenting symptoms, pre-stroke modified Rankin Scale (mRS), wake-up stroke (yes/no), night arrival (i.e., between 6 PM and 6 AM; (yes/no)), and history of prior stroke (yes/no). Covariates were chosen *a priori* based on prior literature of delays to ED arrival. In the main regression model, age was treated as a continuous variable but was converted into a categorical variable for the age-stratified models (age ≤ 60, >60–80, and > 80). The rNIHSS was treated as a categorical variable with 3 levels: ≤5 (mild stroke), 6–12, and 13–42. Living situation was operationalized as living alone versus "other" living situation (living with someone at home, or living in a nursing home or in an assisted living facility). Presenting symptoms were assigned to one of eight categories: focal weakness, focal numbness, decreased level of consciousness, speech difficulties, headache, vision changes, dizziness/vertigo, and "other" (e.g., nausea/vomiting, pain, ataxia, gait difficulty, as well as other symptoms that do not fall into the other seven categories). The "other" category was included in order to capture potentially non-traditional symptoms given literature showing that women are more likely to have non-traditional symptoms than men.[18]

Statistical Analysis

Demographic and clinical characteristics of stroke cases were compared by gender using chi-square tests for categorical data and Wilcoxon rank-sum tests for continuous and ordinal variables. Unadjusted differences in log-transformed time to arrival and arrival within 3 hours of symptom onset between women and men were evaluated using two sample t-tests and chi-square tests, respectively. Multivariable logistic regression, with generalized

estimating equations to account for patients with multiple stroke events during the 2010 study period, was used to evaluate the impact of gender on early arrival (≤ 3 hours from symptom onset to ED). Covariates described above were included in the model. To evaluate the impact of stroke severity and age on the association between gender and early arrival time, patients were stratified by rNIHSS and age categories, and logistic regression was performed in these stratified samples. Adjusted odds ratios with 95% confidence intervals and p-values were reported, with p-values less than 0.05 considered statistically significant. SAS version 9.4 was used for all data analyses.

RESULTS

In 2010, 1991 cases of AIS among residents of the GCNK region presented to an ED; 55% were women, and 22% were black. At admission, a higher proportion of women lived alone (30% vs. 22%, $p < 0.01$). Women had a higher median age (74, IQR 60–84 vs. 67, IQR 57–79, $p<0.01$), and a lower proportion of women had mild strokes compared with men (67% vs. 75%, $p<0.01$) (Table 1).

Prior to adjustment, time to arrival was slightly longer in women (geometric mean 337 minutes [95%CI 307–369] vs. 297 [95%CI 268–329], p=0.05) (Table 1); however, a similar proportion of women and men arrived within 3 hours of symptom onset (24% vs. 27%, p=0.15).

Gender was not associated with delayed time to arrival (aOR=1.00, 95%CI 0.78–1.28) after adjusting for age, NIHSS, and other covariates described above (Table 2). Interactions between gender and age ($p = 0.53$) and gender and NIHSS ($p = 0.34$) were not statistically significant. In the main model, those with mild strokes (aOR 0.49, 95%CI 0.34–0.71) and those who lived alone (aOR 0.56, 95%CI 0.41–0.76) were less likely to arrive within 3 hours of symptom onset (Table 2). Those with pre-stroke mRS of 0 or 1 were more likely to arrive within 3 hours (aOR 1.43, 95%CI 1.10–1.86), as were those who used EMS (aOR 2.66, 95%CI 2.08 – 3.40).

There were multiple significant associations between presenting symptoms and early arrival (Table 2); those with symptoms including numbness, weakness, changes in speech, or changes in vision were more likely to arrive within 3 hours whereas those with decreased level of consciousness were less likely to arrive within 3 hours. “Other” symptoms were not significantly associated with time to arrival in the main model. Among 1051 stroke cases with symptoms categorized as “other,” the most common were nausea/vomiting (25.7%, n=270), ataxia (31.6%, n=332), and non-specific difficulty with gait, balance, or walking (21.9%, n=230). Ninety-eight cases (13.5%) had symptoms of neglect, 68 (6.5%) cases had symptoms of pain, 3.2% (n=31) cases included urinary or bowel incontinence, and 4.0% (n=42) were seizures.

Figure 1 illustrates selected predictors of arrival within 3 hours in our NIHSS-stratified analysis. In addition to gender, the factors shown in Figure 1 are those in which associations with early arrival varied by NIHSS categories. Female gender was not significantly associated with arrival within 3 hours in any of the NIHSS categories. Those with mild

strokes and symptoms categorized as “other” were less likely to arrive within 3 hours (aOR 0.71, 95%CI 0.53–0.94), but among those with moderate or severe strokes, “other” symptoms did not predict earlier arrivals (NIHSS 6 – 12: aOR 0.84, 95% CI 0.46–1.53; NIHSS 13–42: aOR 1.49, 95%CI 0.83–2.67). Having a pre-stroke Rankin score of 0 or 1 predicted arrival within 3 hours in those with mild (aOR 1.57, 95%CI 1.13–2.18) or moderate (aOR 2.08, 95%CI 0.99–4.35) strokes but not in those with severe strokes (aOR 0.92, 95%CI 0.44–1.92).

Figure 2 illustrates selected predictors of arrival within 3 hours in our age-stratified models. In the age-stratified models, gender was not associated with early arrival in any of the three age groups. Living alone was associated with a lower likelihood of arriving within 3 hours for those over 80 (aOR 0.37, 95%CI 0.20–0.65) but not for those in the younger age groups. Finally, numbness and speech changes were only associated with arrival time in those over 80 years of age (Figure 2).

DISCUSSION

In our population-based analysis of factors associated with time to ED arrival in ischemic stroke patients, after adjusting for factors including age, stroke severity, and living arrangements, we found no significant gender difference in arrival within 3 hours of symptom onset. We also found that the relationship between gender and time to ED arrival did not differ significantly across categories of age or stroke severity. Factors that were predictive of delayed arrivals included both social characteristics and characteristics of the stroke itself; we found that patients with mild strokes, those who lived alone, those who did not use EMS, and those who had wakeup strokes were less likely to arrive within 3 hours.

Our study confirms findings from previous literature that women and men have similar times to ED arrival, despite important differences in study populations and settings.[6–11] For example, Lorenzano et al. found similar arrival times by gender in a large European registry that included only those patients treated with tPA. In a recent study of an Austrian stroke registry, women and men had similar symptom onset to door times, but interestingly, women were more likely to have unknown symptom onset times. Gender differences in time to arrival in other previous studies may be a result of a lack of ability to control for confounding variables and the use of different patient selection criteria. For example, unlike our study, some studies showing that women had later arrival times compared with men did not consistently control for living situation or stroke severity.[3,5]

The lack of gender differences in time to ED arrival has important implications for both stroke preparedness campaigns and future research on gender differences in stroke outcomes. The lack of systematic gender differences in time to ED arrival suggests that efforts to increase stroke preparedness and decrease pre-hospital delays should be equally distributed across genders. It does not exclude, however, the possibility of gender differences in the reasons for pre-hospital delays, which further research should address. Though there is extensive evidence showing that women have worse functional outcomes after stroke,[6,11–13] a difference in arrival times is not likely a major contributor to these

disparities in outcomes. Even in those patients in the oldest age group, time to arrival does not seem to a major contributor to poor outcomes in women.

One important predictor of delayed ED arrivals in our study was a low NIHSS on presentation, a finding consistent with prior data.[2,8] We also found that those with symptoms categorized as “other” had an even higher likelihood of arriving late among those with mild strokes. Many symptoms falling into the “other” category in our study are more likely to be associated with posterior strokes; these included nausea/vomiting as well as difficulty with gait and balance. We also observed cases with non-traditional symptoms such as pain and urinary or bowel incontinence. Patients with less severe deficits and non-traditional symptoms, including those like nausea, vomiting, and/or gait difficulty associated with posterior strokes, may not have interpreted their symptoms as warranting immediate attention. The association between mild strokes and later arrival is important to explore further as the majority of AIS [19] in this population are mild, and those with mild strokes are at high risk for poor outcomes.[20,21] To ensure that even those with mild strokes are eligible for time-sensitive therapies, future educational interventions should teach patients and bystanders to seek medical care immediately, even if symptoms are mild or non-traditional.

Our findings are consistent with our group’s prior work on predictors of EMS use among acute stroke patients.[22,23] In a prior study of approximately 3000 stroke patients, women and men were equally likely to use EMS to access care. As EMS use is highly associated with faster arrival times,[8,9] it follows that data on gender and EMS use would be similar to the data on gender and arrival times. One difference between the current study and previous work on factors associated with EMS use relates to pre-stroke disability; higher pre-stroke disability was associated with an increased likelihood of using EMS in our previous study[22] but was found to be associated with longer arrival times in the current study. It may be that limited mobility or other factors associated with pre-stroke disability led to delays in calling EMS and overall delayed ED arrival times. Another difference between the current study and our group’s previous work is the effect of decreased level of consciousness on hospital arrival. Previously, we reported that stroke patients presenting with a decreased level of consciousness were more likely to use EMS,[23] but in the current study patients with a decreased level of consciousness were less likely to arrive within 3 hours of onset. Though EMS use is typically associated with shorter arrival times, our finding that those with decreased mental status took longer to arrive may be due to patients having to wait for a bystander to discover the event and call 911.

Other findings from our age-stratified analysis suggest that age influences the association between certain presenting symptoms and ED arrival times. Specifically, the presence of speech changes and numbness had progressively stronger effects on arrival times with increasing age. In patients under 60 years of age, these presenting symptoms did not predict arrival within 3 hours, while in those over 80, there was a strong association between each of these symptoms and arrival within 3 hours. While these data are hypothesis-generating only, these findings may represent different interpretation of stroke symptoms across age groups, and further research is warranted. Age also influenced the relationship between living alone and delayed ED arrival. Living alone was only an important predictor of

delayed arrivals among those over 80, pointing to a need for increased social support in older patients at risk for stroke.

LIMITATIONS

First, some patients had undocumented symptom onset or last known normal times. In order to reflect clinical practice, patients with an unknown time to arrival were assumed to have arrived after 3 hours of symptom onset. There is a potential for misclassification bias, but bivariate analyses of time to ED arrival as a continuous variable (which excluded those with unknown times) produced similar results. In regards to our age- and stroke severity-stratified analyses, these were exploratory in nature, and could have been subject to Type II error in some of the categories with smaller numbers of patients. Finally, our data is from 2010, but it is doubtful that arrival times have changed significantly since in the interim; in addition, other recently published literature on arrival times among stroke patients has evaluated similar time periods.[10]

CONCLUSIONS

In this population-based analysis of gender and time to ED arrival among ischemic stroke patients, we found no significant differences between women and men, even across categories of age and stroke severity. Important patient characteristics that were associated with delays and should be evaluated further included living alone and having mild strokes. Given the lack of a significant difference in arrival times between women and men, further research to identify the contributors to poor outcomes in women with stroke is needed.

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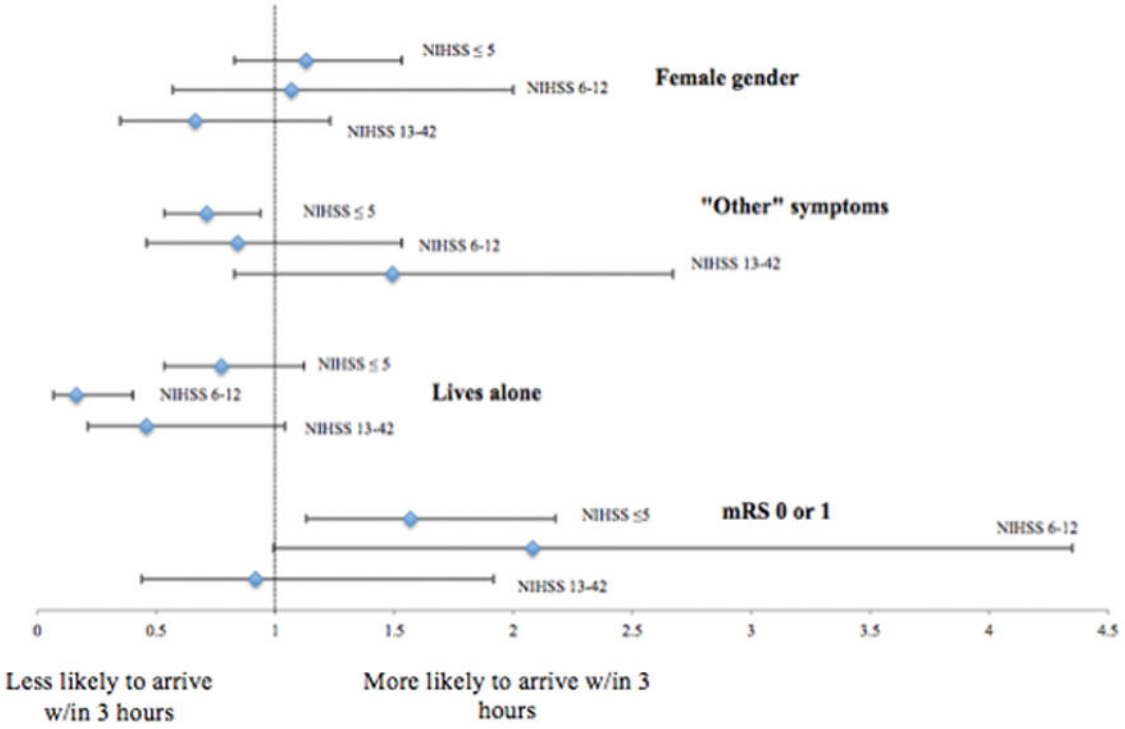

Figure 1.

Selected Predictors of Arrival within 3 Hours, Stratified by NIHSS

NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin score

Point estimates are the adjusted odds of arriving within 3 hours of symptom onset, stratified by NIHSS. Other variables included in the models but not shown in the figure included age, race, insurance status, additional presenting symptoms, marital status, use of EMS, night arrival, wake-up stroke, and history of prior stroke.

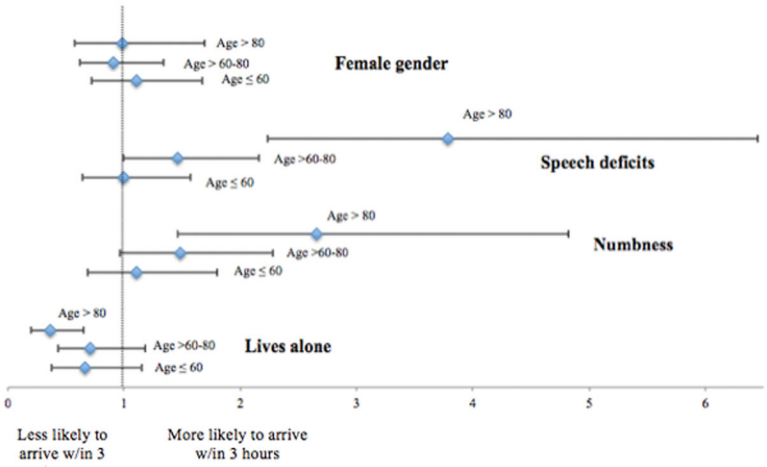

Figure 2.

Selected Predictors of Arrival within 3 Hours, Stratified by Age

Point estimates are the adjusted odds of arriving within 3 hours of symptom onset, stratified by age. Other variables included in the models but not shown in the figure included race, NIHSS, insurance status, additional presenting symptoms, marital status, use of EMS, wake-up stroke, night arrival, pre-stroke modified rankin score (mRS) 0 or 1, and history of prior stroke.

Table 1

Baseline characteristics of stroke cases

	Women (N=1097)	Men (N=894)	p-value
Age, median, IQR	74 (60, 84)	67 (57, 79)	<0.01
Black Race	248 (23%)	181 (20%)	0.20
Insured	964 (88%)	750 (84%)	0.01
Presenting Symptom			
Weakness	799 (73%)	665 (74%)	0.44
Numbness	383 (35%)	371 (41%)	<0.01
Decreased LOC	518 (47%)	333 (37%)	<0.01
Speech	740 (67%)	544 (61%)	<0.01
Headache	282 (26%)	189 (21%)	0.02
Vision	251 (23%)	200 (22%)	0.79
Dizziness/vertigo	180 (16%)	181 (20%)	0.03
Other	572 (52%)	479 (54%)	0.53
NIHSS			
≤5	734 (67%)	667 (75%)	<0.01
6–12	192 (17%)	116 (13%)	
13–42	171 (16%)	111 (12%)	
Lives alone	324 (30%)	200 (22%)	<0.01
EMS arrival	476 (43%)	393 (44%)	0.80
Pre-stroke mRS, median (IQR)	2 (0, 3)	1 (0, 2)	<0.01
Pre-stroke mRS 0–1	424 (39%)	496 (55%)	<0.01
Wake-up stroke	235 (21%)	173 (19%)	0.25
Night arrival	317 (29%)	272 (30%)	0.46
History of prior stroke	288 (26%)	242 (27%)	0.68
Marital status			<0.01
Married/living with partner	337 (31%)	500 (56%)	
Single	145 (13%)	133 (15%)	
Widowed/divorced/separated	610 (56%)	257 (29%)	
Unknown	5 (.5%)	4 (.5%)	
Time to arrival, minutes, geometric mean (95% CI)	N=807 337 (307, 369)	N=657 297 (268, 329)	0.052
Time to arrival ≤ 3 hours	268 (24%)	244 (27%)	0.15
Unknown time to arrival	290 (26.4%)	237 (26.5%)	0.97

P-values for differences between women and men are from chi-square tests for categorical/binary data and from Wilcoxon rank-sum tests for continuous and ordinal variables.

IQR: Interquartile range, LOC: level of consciousness, NIHSS: National Institute of Health Stroke Scale, EMS: Emergency medical services, mRS: Modified rankin score

Table 2

Predictors of arrival within 3 hours

	Unadjusted OR			Adjusted OR		
Variable	**OR**	**95%CI**		**OR**	**95% CI**	
Female gender	0.86	0.70	1.05	1.00	0.78	1.28
Age (per year)	1.00	1.00	1.01	1.01	1.00	1.02
NIHSS						
≤5	0.37*	0.29	0.49	0.49*	0.34	0.71
6–12	0.54*	0.38	0.76	0.69	0.46	1.03
13–42	Ref					
Presenting Symptoms						
Weakness	1.73*	1.35	2.21	1.34*	1.01	1.78
Numbness	1.54*	1.25	1.88	1.67*	1.29	2.14
Decreased LOC	1.00	0.82	1.23	0.60*	0.45	0.79
Speech	1.90*	1.52	2.39	1.54*	1.17	2.02
Headache	0.86	0.67	1.1	0.99	0.73	1.35
Vision	1.30*	1.03	1.64	1.35*	1.02	1.78
Dizziness/vertigo	0.88	0.68	1.15	1.18	0.86	1.63
Other	0.82	0.67	1.01	0.83	0.66	1.05
Black race	0.88	0.68	1.13	0.91	0.68	1.22
Insured	1.12	0.83	1.52	1.21	0.82	1.80
Married	1.36*	1.11	1.67	1.10	0.83	1.45
Lives alone	0.62*	0.49	0.80	0.56*	0.41	0.76
EMS arrival	2.61*	2.13	3.20	2.66*	2.08	3.40
Wake-up stroke	0.04*	0.02	0.09	0.03*	0.02	0.07
Night arrival	1.97*	1.60	2.44	1.70*	1.34	2.16
Pre-stroke mRS 0 or 1	1.14	0.93	1.39	1.43*	1.10	1.86

	Unadjusted OR			**Adjusted OR**		
Variable	**OR**	**95%CI**		**OR**	**95% CI**	
History of prior Stroke	1.02	0.82	1.28	0.95	0.73	1.24

* indicates statistically significant odds ratios (p<0.05).